Progress in the Psychobiology of Post-traumatic Stress Disorder: An Overview

It has been a pleasure to serve as Guest Editor for this issue of *Seminars in Clinical Neuropsychiatry,* Progress in the Psychobiology of Post-traumatic Stress Disorder (PTSD). This is the third publication devoted entirely to this topic; the first 2 books were published in 1995 and 1997.[1,2] It is useful to consider the focus of these 3 publications as a way to appreciate the rapid conceptual and empirical advances in our emerging understanding of the psychobiology of PTSD.

In 1993, when Dennis Charney, Ariel Deutch, and I began to outline the sections and chapters for *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder,*[1] there were relatively little empirical data on the psychobiology of PTSD, and most of that had been obtained from research with Vietnam veterans. There were robust psychophysiological findings, a small but compelling body of information on adrenergic, hypothalamic-pituitary-adrenocortical (HPA) and thyroid abnormalities, and a confusing array of studies on sleep. That was as far as laboratory research on people with PTSD had gone. I doubt that we would have moved forward to produce that book if we hadn't shared a theoretical belief, that PTSD could be best understood within the broader context of coping and adaptation. Unlike other psychiatric disorders, we argued, research pertinent to PTSD had its genesis in the seminal insights of Walter Cannon[3] and Hans Selye.[4] Therefore, our book had many chapters on stress research with animals and on theoretical models of the impact of stress on brain function. We were convinced that such research was relevant to the ultimate understanding of the pathophysiology of PTSD and saw our book as a starting point for implementation of a research agenda, in which clinical researchers would investigate PTSD from this theoretical perspective and in which basic scientists would "test laboratory paradigms that are informed by clinical observations and questions".[1]

The second book, *Psychobiology of Posttraumatic Stress Disorder*[2] grew out of an extraordinary conference organized by Rachel Yehuda and Alexander McFarlane under the aegis of the New York Academy of Sciences in 1996. By then, there were more data to present from studies with PTSD subjects who were not Vietnam veterans. Findings previously generated by only one group of investigators had, by now, been successfully replicated in several laboratories. There were important advances in research on psychophysiology, adrenergic mechanisms, the HPA axis, and sleep. Of equal importance was the emergence of exciting data in new areas such as structural and functional brain imaging, the neurobiological basis of traumatic and nontraumatic memory impairment, and neurodevelopmental effects of trauma. In addition, conceptual models, now enriched by clinical observations, focused on the hippocampus, the amygdala, neuroplasticity, and a growing number of animal models for PTSD.

The articles in this issue represent another step forward in our emerging understanding of the psychobiology of PTSD. Given the page limitations, it was frankly very difficult to squeeze in all the new conceptual and empirical advances that have been made in recent years. I have not been able to include everything, but I believe these articles collectively provide an excellent overview of our field at this time. The introduction to each article will be my way of telling you what I consider the most important and exciting developments in each area of investigation.

Psychophysiological research, reviewed by Roger Pitman and colleagues, encompasses studies on psychophysiological reactivity to trauma-related stimuli, the startle response, event-related electroencephalographic potentials (ERPs), and sleep. These paradigms lend themselves very well to protocols designed to investigate different aspects of information processing. Current research suggests that PTSD subjects may be more "conditionable," more resistant to extinction, and more prone to sensory, cognitive, and affective processing abnormalities marked both by impairments in memory and concentration and by heightened selective attention to trauma-related or threatening stimuli.

The article on neuropharmacology by Steven Southwick and colleagues provides more elegant data regarding adrenergic dyscontrol in PTSD, exemplified especially by clinical and cerebral metabolic abnormalities elicited by challenge with the adrenergic alpha-2 antagonist, yohimbine. In addition, this article presents important new animal and human data on serotonergic mechanisms. This has been a major gap in our understanding of PTSD up to now, especially because the most effective current therapeutic agents seem to be selective serotonin reuptake inhibitors.

Research on the HPA axis, reviewed by Rachel Yehuda, represents some of the most elegant work in our field. Her observations, now replicated in other laboratories, show that with respect to HPA function, PTSD has a unique pathophysiology that distinguishes it from major depressive disorder. The article also presents an intriguing hypothesis of how HPA-enhanced negative feedback caused by supersensitive glucocorticoid receptors might have contributed to reduced hippocampal volumes in PTSD subjects.

Douglas Bremner reviews the growing research literature on brain imaging that shows structural and functional abnormalities in PTSD subjects. Findings on reduced hippocampal volume seem to be associated with

decrements in learning and memory. In addition, reduced activation in the anterior cingulate and medial orbitofrontal cortex may explain why PTSD subjects exhibit resistance to extinction in psychophysiological studies reviewed earlier by Pitman and colleagues.

The other 4 articles address what I consider the most important theoretical issues for the future. I was particularly eager to emphasize research areas in which activity has recently intensified because of current clinical concerns. Among these I include memory processing in PTSD, dissociation as an integral part of the PTSD syndrome, stress-induced neuroplasticity exemplified by behavioral sensitization models of PTSD, and PTSD as a risk factor for poor physical health.

Because of the so-called "recovered memory controversy," intense media and forensic attention has focused on the accuracy of traumatic memories (especially those related to childhood sexual abuse) reported by individuals with PTSD. Such clinical and forensic issues have spurred research on the basic memory mechanisms of acquisition, consolidation, and retrieval; on whether the brain processes traumatic memories differently than nontraumatic memories; on how memory function is affected by specific biological systems; and on the clinical implications of these factors. Larry Cahill's article approaches this rich theoretical and controversial area with a specific focus on the crucial role of the amygdala in memory storage of emotional events.

Dissociation has recently drawn greater attention by researchers because of our emerging recognition that it is an important part of the PTSD syndrome. Although not explicitly identified among the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for PTSD, dissociation is so identified in the World Health Organization's International Classification of Diseases, 10th Edition (ICD-10) criteria for PTSD and in the DSM-IV criteria for Acute Stress Disorder. More importantly, people who experience peritraumatic dissociation during exposure to a traumatic event seem to be at greater risk to develop PTSD than those who do not.[5] As originally proposed by Krystal et al[6] and now updated by Andrew Chambers and colleagues, dissociation seems to be a psychobiological alteration in glutamatergic mechanisms that produces clinically significant distortions in perception, learning, and memory. Understanding such abnormalities may not only be a key to unraveling the pathophysiology of PTSD but also to developing new pharmacological approaches for this disorder.

PTSD seems to be the result of stable alterations in brain function produced by exposure to a catastrophic event that overwhelms an individual's psychobiological adaptive capacity. It can be explicated in terms of classical and operant learning paradigms in which fear conditioning and resistance to extinction are sustained by neuroplastic alterations in key brain systems (especially the amygdala and hippocampus) that mediate implicit and explicit memory functions. At the neuronal level, some of these phenomena can be understood in terms of sensitization models first proposed by Robert Post and associates for bipolar illness and more recently applied to PTSD.[7] In this issue, Post and colleagues launch their rich conceptual article from the perspective of cocaine-induced sensitization and maternal deprivation animal models. They show how stress might trigger a cascade of alterations in gene expression affecting many different neurotransmitter systems. Furthermore, they show that such changes are not static, but progress longitudinally through a series of stages, each of which might be associated with a different pattern of neuronal abnormalities. From a clinical perspective, this has the very important implication that different drugs might be needed to normalize different stages in this evolving process; certain drugs might be prescribed prophylactically before trauma exposure, others immediately after traumatization, and still others for later stages of PTSD.

The final article by Paula Schnurr and Kay Jankowski on physical health in PTSD offers a very different perspective on how clinical experience is affecting theory and must ultimately affect clinical practice. Based on our review of the literature, Paula Schnurr and I had previously proposed that exposure to trauma was associated with poor health outcomes.[8] We further speculated that this relationship was mediated by PTSD, although there were very little empirical data at the time to fortify this hypothesis. This chapter reviews newer findings that are consistent with our previous proposal that there may be an association between PTSD and poor health outcomes. Such findings have stimulated new research on how psychological, behavioral, and biological abnormalities associated with PTSD increase the risk for poor physical health. Such findings also necessitate alterations in current clinical practice patterns so that screening for PTSD can be carried out routinely in primary or specialty medical practice settings where PTSD patients most frequently seek treatment.

The final point I wish to emphasize is how investigators working in different areas have begun to converge in their conceptual and empirical interests. As a result, each article in this issue is much more integrative and broader in scope than was the case in the 2 books on the psychobiology of PTSD published previously. In each of those publications, a chapter on psychophysiology was only concerned with psychophysiology; one on adrenergic systems only focused on adrenergic mechanisms, HPA function on HPA function, and so forth. That is not the case in the present publication. For example, the article on psychophysiology raises questions about sensitization and information processing. The article on HPA function generates an intriguing hypothesis on how HPA abnormalities produce the smaller hippocampal volumes observed in PTSD.

The article on brain imaging addresses key questions about information processing, explicit memory function, and altered neural processes that may be responsible for resistance to extinction. The article on memory presents data about adrenergic mechanisms. The article on physical health incorporates psychophysiological, neuropharmacological, and neuroendocrinological findings. The article on dissociation focuses on memory and sensitization while presenting an integrated model of information processing that postulates abnormal interactions between 5 different neurotransmitter systems. And the article on sensitization has implications for material covered throughout this entire issue.

As our empirical findings grow, our conceptual framework must also expand. Work on memory, dissociation, sensitization, and physical health is in its infancy. There are other relatively unexplored areas for future research that will undoubtedly receive greater attention in future volumes of this sort. The most important of these concern risk factors for PTSD and whether people who develop this disorder are different in some fundamental psychobiological characteristic.[9] Yehuda has assembled our current knowledge on this question[10] and raised the chicken-or-egg question: which came first, the psychobiological abnormality or the PTSD? In the present issue this question is addressed most prominently with regard to the smaller hippocampal volume found in individuals with PTSD: is the smaller hippocampal volume the result of PTSD or were such people more vulnerable to develop PTSD because of a preexisting smaller hippocampus? Likewise, do people with enhanced glucocorticoid receptor sensitivity develop such an abnormality after they develop PTSD or was it present beforehand? And does abnormal glucocorticoid receptor sensitivity, whether inherent or acquired, have anything to do with smaller hippocampal volume? Such questions have begun to spawn intriguing quasiprospective approaches such as twin studies, use of archival databases, and other longitudinal designs.

There are other important questions raised in this issue that receive little or no mention because empirical data are lacking at present. Pitman, Orr, and associates have begun to investigate another heuristically rich chicken-or-egg question: are people with PTSD more "conditionable" than others or did such "conditionability" make them more vulnerable to develop PTSD in the first place? Southwick and associates review a neuropharmacological literature that has grown from an exclusive focus on the adrenergic system to include research on serotonergic function, whereas Chambers and associates emphasize the crucial role of glutamatergic transmission; but there is still very little information on other neurotransmitters and neuropeptides such as dopamine, gamma-aminobutyric acid (GABA) opioids, corticotropin-releasing-factor (CRF), neuropeptide Y, substance P, and cytokines that play an important role in the human stress response. Basic research pertinent to PTSD as a risk factor for physical health has only begun to explore immunologic function in people with this disorder. And neuroendocrine research must investigate thyroid, growth hormone, prolactin, gonadotropin, and posterior pituitary hormone function.

To identify such important growth areas for future research is not to minimize the rapid progress that has been achieved in this young field of inquiry. We have moved light-years beyond Abram Kardiner's brilliant paradigm shift almost 60 years ago when he moved beyond psychoanalytic formulations to coin the term "physioneurosis" to explain the physiological hyperreactivity he observed in veterans of World War I.[11] PTSD has clearly established itself as a unique disorder expressed through abnormalities in fundamental psychobiological mechanisms concerning learning, memory, coping, and adaptation. Robust and clinically relevant findings are emerging in a number of key psychobiological domains. And we have recently come to a stage where investigators, working in different areas, have begun to converge conceptually to integrate their various findings.

Perhaps we no longer resemble the 6 blind men each trying to conceptualize the elephant's true morphology from his own fixed perspective. Perhaps we are starting to perceive the enormity and complexity of the many psychobiological abnormalities associated with PTSD. Perhaps we are beginning to understand how each crucial part relates to the others and how such emerging knowledge must guide future research and clinical initiatives. If so, it is but a modest step. A step that is part of a long procession. But it is one more step in the right direction.

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